REMARKS/ARGUMENTS

I. Status of the Claims:

Prior to entry of this amendment, claims 31, 32, 35-37, 39-41 and 43-73 were pending in the application, with claims 45-63 withdrawn as directed to a non-elected invention. Upon entry of this amendment, certain claims are amended, and claims 70 and 71 canceled, without prejudice or disclaimer. New claims 74-78 are introduced upon entry of this amendment. Thus, claims 31, 32, 35-37, 39-41, 43-69, and 72-78 are pending following entry of this amendment, with claims 45-63 withdrawn from consideration.

The amended and new claims find support throughout the specification including, for example, the following sections: page 5, lines 8-9, and lines 20-23; and page 10, first and second complete paragraphs.

II. Claim Rejections under 35 U.S.C. § 102:

Claims 31-32, 35-37, 39-40, 43-44, 66-69 and 72-73 are rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,408,039 to Burnouf-Radosevich ("Burnouf-Radosevich"). The basic argument made in the Office Action is that while Burnouf-Radosevich discusses methods for generating high purity vWF compositions that these compositions may nonetheless contain trace amounts of propeptide and/or pro-vWF. Since the claims are directed to preparations "comprising" propeptide or pro-vWF, it is asserted that any amount of propeptide or pro-vWF meets the limitations of the claims.

Applicants in prior responses have explained in detail why the compositions discussed in Burnouf-Radosevich do not *"necessarily"* contain either the propeptide or pro-vWF as required to establish anticipation on the basis of inherent properties (see MPEP 2112). Certain claims, nonetheless, have been amended to clarify the nature of the presently claimed invention, with the

goal of advancing prosecution of subject matter of current commercial importance, not because Applicants agree that the Office has satisfied its burden of demonstrating inherency.

For instance, claim 31 and 67 have respectively been amended to state that preparation comprises a "pharmaceutically effective amount" of vWF propeptide or pro-vWF. Claim 64 has been amended to independent form and recites that the vWF propeptide is at least 80% pure. The Examiner has indicated that a claim in this form should be free of the prior art. New claims 75 and 77 respectively state that the propeptide and pro-vWF concentration is at least 10 nM.

To reject a claim as anticipated, the Patent Office must show that "each and every element as set forth in the claim is found, either expressly or inherently" in a single prior art reference (see MPEP 2131.01; Verdegaal Bros. V. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). As emphasized in prior responses, when, as here, the Patent Office attempts to demonstrate that a reference inherently anticipates a claim, the Patent Office must overcome a substantial burden. The Federal Circuit has specifically stated:

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' (MPEP 2112; citing In re Robinson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-1951 (Fed. Cir. 1999) (emphasis added).

It is submitted that Burnouf-Radosevich fails to describe each element of the present claims, either expressly or inherently. As the Office acknowledges in the current response, Burnouf-Radosevich focuses on methods of preparing a "highly purified vWF concentrate"

(Office Action at page 4, last sentence). Under the foregoing inherency standard articulated by the Federal Circuit, the burden is thus on the Office to *clearly establish* that this "highly purified" vWF composition nonetheless *necessarily* satisfies each element of the presently claimed preparations. The Federal Circuit has emphasized that this standard is not satisfied by establishing probabilities or possibilities. As indicated above, it is also noted that the Examiner has indicated that claims that specify a purity level such as in claims 64, 65 and 74 are not anticipated by Burnouf-Radosevich (Office Action at sentence bridging pages 6 and 7). Although the current amendments and foregoing arguments are deemed sufficient to address the rejection, the specific concerns listed in the Office Action are nonetheless addressed.

A. vWF-Propeptide

One concern expressed in the Office Action is that the highly purified vWF compositions discussed by Burnouf-Radosevich may still contain trace amounts of vWF-propeptide. The Office Action cites Fujisawa (Eur. J. Biochem. (1981) 196:673-677) and Ruggeri et al. (Thrombosis and Haemostasis 67:594-599 [*Ruggeri*]) for the proposition that the propeptide is present in plasma (Office Action at page 6). However, whether propeptide is present in a *collected plasma sample* is not the issue. The issue, is *whether a plasma sample that has been purified as described in Burnouf-Radosevich would necessarily contain vWF-propeptide as recited in the current claims*. The Office cannot satisfy its burden under the inherency standard simply by pointing to certain statements that some collected plasma samples contain vWF-propeptide. Instead, the Office must *clearly establish* that the "highly purified" composition described in Burnouf-Radosevich nonetheless *necessarily* contains vWF-propeptide as recited in the current claims directed to vWF-propeptide compositions (e.g., claims 31, 64 and 75 and their dependent claims).

A complete review of the references that have been cited or submitted makes clear that the Burnouf composition does not satisfy each element of the presently claimed vWF-propeptide compositions. As pointed out in the previous response, the vWF-propeptide plasma concentration is only about one-tenth that of vWF plasma concentrations. Moreover, the half life

of vWF-propeptide is substantially less than that for mature vWF (2-3 hours versus 12 hours, respectively) (see, e.g., Turecek, et al. (1999) Blood 94:1637-1647 at page 1637, col. 1 last line to col. 2, line 4 ["*Turecek I*"]; see also, Varadi, et al. (2001) Thromb. Haemost. 86:1449-1458, page 1449, col. 2, first full paragraph ["*Varadi*"]). As described in the last response, to obtain the composition that the Office says anticipates the current claims requires a minimum of 20 hours (likely considerably longer). This is equivalent to approximately 7 to 10 vWF-propeptide half lives. Any vWF-propeptide present in the composition obtained after this lengthy procedure, a composition which the Office itself refers to as a "highly purified vWF concentrate," would not correspond to a "pharmaceutically effective amount" as recited in base claim 31 or satisfy the purity or concentration requirements set forth in base claims 64 and 75, respectively. Even if one assumes, arguendo, that the Burnouf-Radosevich composition includes a contaminating amount of vWF-propeptide as the Office contends, the trace amount present would not be expected to show any significant and/or reliable and/or predictable pharmaceutical effect. There certainly is no evidence to suggest that any trace amount of vWF-propeptide in the Burnouf-Radosevich composition would be present at the concentrations or purity recited in claims 64 and 75.

On page 7 of the Office Action, it is argued that vWF-propeptide would be present in the Burnouf-Radosevich composition regardless of whether the vWF-propeptide is associated with mature vWF. The rationale for this argument is that vWF-propeptide necessarily must be present in a vWF composition because of the difficulties in purifying these two proteins from one another. This difficulty is attributed to vWF-propeptide being highly homologous to vWF.

This, however, simply is not the case. Although the vWF-propeptide and vWF are both components of pro-vWF, the vWF-propeptide is distinct from vWF and these two proteins have low sequence homology. A sequence alignment analysis conducted using the database http://us.expasy.org indicates that there is only about 30-40% sequence identity, and this only over limited regions of the two proteins.

To further bolster the argument regarding the difficulty in separating vWF-propeptide and vWF, the Office Action first states that the purification process in Burnouf-Radosevich

primarily involves anion exchange chromatography. However, since the scientific literature appears not to discuss methods for separating vWF-propeptide and vWF by anion exchange chromatography, it is concluded that these proteins cannot be separated in this manner. This in turn is said to mean that the "highly purified vWF concentrate" obtained by Burnouf-Radosevich must nonetheless contain vWF-propeptide.

There are several problems with this analysis. First, if the proteins could not be separated by anion exchange, one would expect the isoelectric points (pI) for these two proteins to be very similar, as this parameter is the most relevant parameter for determining the ability of a protein to bind to an anion exchange column. However, using standard calculation tools at http://us.expasy.org, the isoelectric point (pI) of vWF-propeptide and vWF were respectively calculated to be 5.06 and 5.41, a difference sufficient to separate the two proteins by anion exchange chromatography. Second, it cannot be concluded that the proteins are incapable of being separated by anion exchange chromatography simply because such a purification has not been described previously; such an argument merely attempts to establish a positive by trying to prove a negative. Third, this analysis ignores the preceding point, namely that any vWF-propeptide initially present in the plasma from which the Burnouf-Radosevich composition is purified would be reduced to levels below the levels recited in the present claims due to the fact that the time to purify the composition takes at least 7-10 vWF-propeptide half lives.

B. pro-vWF

The Office Action at pages 8-9 continues to point to sections from Wise et al. (Cell 52:229-236, 1988) and Ruggeri to support the contention that pro-vWF is circulating in vivo. But whether pro-vWF is circulating in vivo is not the issue, as it does not follow that pro-vWF would still be present in the Burnouf-Radosevich vWF composition, which is obtained after a lengthy and complex purification. To demonstrate inherent anticipation of the present claims to pro-vWF compositions, the burden is on the Office to *clearly establish* that the "highly purified" Burnouf-Radosevich vWF concentrate *necessarily* includes pro-vWF at the concentration levels currently recited in base claims 67 and 77. The Office Action falls well short of meeting this

burden. Even if one assumes, arguendo, that a certain level of pro-vWF is present in vivo in the circulation, the Office has failed to demonstrate that pro-vWF, particularly a pharmaceutically effective amount, would *necessarily* still be present after the freezing, thawing, centrifugation, aluminum hydroxide purification and viral inactivation steps required to obtain the Burnouf-Radosevich composition. This is what the Office must show to establish inherent anticipation of the current claims and thus far has failed to do.

The Office has also not addressed the full teaching of the references currently under consideration. In particular, the Office has not addressed at least two additional key points made in the scientific literature regarding the stability of pro-vWF once secreted into the circulation:

1. Various articles note that although pro-vWF is secreted into the circulation that it "is detectable in normal human plasma only on rare occasions, and even then only trace amounts are observed" (see, e.g., Turecek I, at page 1637, col. 2, lines 6-8; Varadi, at page 1449, col. 2, 4th sentence of second complete paragraph; and Turecek et al. (2002) Histochem. Cell Biol., 117:123-129, at page 124, second col., last three sentences [*"Turecek II"*]); and

2. Studies with animal model studies in which recombinant pro-vWF was intravenously injected demonstrate that pro-vWF is quickly metabolized in the circulation (Turecek I at abstract; page 1637, second column, last paragraph; and page 1644, first column, last paragraph; and Varadi, at page 1449, second column, second to last paragraph of introduction).

The available evidence then is clear that pro-vWF released into the circulation is rapidly degraded to concentration levels that are rarely detectable. As such, the Burnouf preparation would not *necessarily* contain pro-vWF, particularly at the levels recited in current base claims 67 and 77. This is particularly true given the length of time (as noted above, at least 20 hours) necessary to obtain the Burnouf-Radosevich vWF concentrate.

III. Rejections under 35 U.S.C. § 103(a):

Claims 31, 32, 39, 40, 43-44, 64-65 and 72 are rejected under 35 U.S.C. § 103(a) as obvious over an article by Takagi et al. (J. Biol. Chem. 264:6017-6020, 1989; hereinafter "Takagi") in view of EP 131740 to Neurath (hereinafter "Neurath") and an article by Blann et al. (Eur. J. Vasc. Surg. 8:10-15, 1994; hereinafter "Blann").

Takagi is said to disclose a composition containing purified vWF-propeptide. It is acknowledged, however, that Takagi does not teach or suggest vWF-propeptide compositions that have been treated for at least one of viral inactivation or virus removal and that is suitable for therapeutic administration. Neurath is said to discuss methods for making compositions that are free of certain viruses. The combined discloses of Takagi and Neurath is said to render the foregoing claims obvious.

The motivation for making the combination is said to be found in the combined discussion of Takagi and Blann. Blann is said to discuss how increased vWF levels are correlated with various risk factors for atherosclerosis and arterial disease. The Office Action also states that Blann suggests that in view of such correlations that future therapies for treating atherosclerosis and arterial disease might use agents that inhibit vWF activity. Since Takagi is said to discuss the possibility that vWF-propeptide might have an effect on hemostasis that opposes that of mature vWF (e.g., inhibition of collagen-induced aggregation of human platelets), the Office Action concludes that one of skill in the art would have been motivated to combine the purified vWF-propeptide compositions of Takagi with the viral inactivation methods of Neurath to obtain pharmaceutical compositions useful in treating individuals at risk for atherosclerosis or arterial disease because of elevated vWF levels. For the reasons that follow, Applicants respectfully disagree.

A. No Motivation to Combine the Cited References

To establish a prima facie case of obviousness, the Office is obligated to provide "evidence of the motivating force that *impels* one skilled in the art to do what the patent applicant

has done (Ex parte Levengood, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) (emphasis added). As just noted, the Office Action contends that the requisite motivation is provided by the discussion in Blann indicating a need for preparations that oppose the negative effects on arteries associated with elevated vWF levels and the discussion in Takagi indicating that vWF-propeptide and mature vWF might have opposing effects with respect to platelet adhesion to the subendothelium of arteries.

This rationale, however, presumes that Blann teaches that vWF is a *causative agent* in atherosclerosis or other arterial diseases. But this is not the case. Instead, Blann explicitly states that there is *insufficient* information to conclude that elevated vWF levels have a causative effect. Examples of Blann's conclusions regarding the causal effect of vWF on arterial disease include the following:

> "Hence, there is *no data* in humans which would allow us to conclude that von Willebrand disease [i.e., low vWF levels] protects from atherosclerosis." (Blann at page 13, col. 1, last sentence of the first full paragraph; emphasis added).
>
> "There is clearly more scope for studies which seek to explain raised levels of vWF and their association with disease." (Blann at page 13, col. 1, last sentence).

These statements unambiguously demonstrate: 1) an absence of evidence that would enable one to conclude that high vWF levels were a potential cause of arterial disease, and 2) that further investigation was needed to understand the association between high vWF levels and diseases such as atherosclerosis. At best, Blann simply concludes that vWF may serve as a *marker* for arterial disease. But a protein can be a marker without being a causal factor in disease. This conclusion is distinct from the conclusion reached in the Office Action, namely that high vWF levels are a *causal* factor of arterial disease, which, if opposed, would be of therapeutic value.

The Examiner cites a sentence from the final paragraph for the proposition that Blann suggests that future therapeutic strategies could involve agents that oppose vWF. The sentence in question, however, in its entirety reads:

> "It *may* be that *future studies* will recommend that the aim of clinical treatment be reduction in vWf levels and so may be the object of novel therapeutic approaches." (Blann at page 13, col. 2, second sentence of last paragraph; emphasis added).

Even this statement makes clear that Blann considered there to be insufficient evidence to support the hypothesis that a reduction of vWF levels would convey a therapeutic effect. Instead, Blann speculates that perhaps *future studies* would provide the data necessary to support such an association.

Turning from the discussion in Blann to that in Takagi, the rationale for the motivation presented in the Office Action presumes that the *in vitro* results Takagi discusses indicating that pp-vWF has collagen inhibitory activity necessarily applies *in vivo*. Takagi, however, does not make this assumption. Instead, Takagi notes only that there is a possibility that the collagen binding observed in the *in vitro* experiments conducted might be physiologically relevant (see, e.g.; page 6018, col. 2, first full paragraph and page 6019, last two sentences).

So individually and collectively the statements from Blann and Takagi fall well short of providing a motivation that would *impel* one to make the compositions that are currently claimed as required to establish a prima facie case of obviousness. Instead, the disclosure in these two references at most simply provide an invitation to conduct research to establish that which the Office Action presumes, namely that elevated vWF levels are a causal factor in arterial disease and that the collagen binding activity of pp-vWF observed in vitro is physiologically relevant. Therefore, the motivation presented in the Office Action is at best an "obviousness to try rationale," a rationale that has been discredited by the courts as insufficient to satisfy the requirements for establishing motivation (see MPEP 2145).

B. No Reasonable Expectation of Success

The Office Action also fails to establish a prima facie case of obviousness because one skilled in the art would not have had a reasonable expectation of success of obtaining a useful composition based upon the disclosure of the prior art of record.

Applicants first reiterate a point made in the last response (see, e.g., pages 5 and 6) but not addressed in the current Office Action. This point is that the art of record describes how pro-vWF and vWF-propeptide are both relatively rapidly degraded in the circulation [With respect to pro-vWF see, e.g., Turecek I at page 1637, col. 2, lines 6-8; Varadi at page 1449, col. 2, 4th sentence of second complete paragraph; and Turecek II, at page 124, second col., last three sentences. With respect to vWF-propeptide, see, e.g., Turecek I, at page 1637, col. 1, last line to col. 2, line 4; and Varadi, page 1449, col. 2, first full paragraph]. In view of such discussion, one of ordinary skill would not have had a reasonable expectation that pro-vWF and/or vWF-propeptide could effectively be used as a therapeutic because their relatively short life span in the circulation would not be sufficient to confer a benefit.

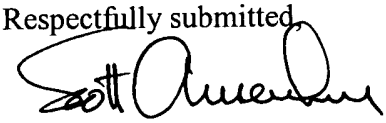
Secondly, the picture that emerges from Blann is that arterial disease is a very complex disease, being associated with a number of risk factors (e.g., smoking, diabetes, hyperlipidaemia, hypertension and obesity) and linked to a variety of potential causative agents (ketoacidosis, oxygen radicals and oxidized low density lipoprotein in hypercholesterolaemia) (see, e.g., Blann at page 12). Contrary to the rationale presented in the Office Action, at no point does Blann indicate that there is evidence supportive of the view that high vWF levels *cause* arterial disease in humans. In fact, as noted above, Blann instead concludes that there was at the time "no data" to support such a conclusion (Blann at page 13, col. 1, last sentence of first full paragraph). So, in view of the extensive list of factors other than vWF for which Blann suggests a causal role, coupled with the explicit statement that such evidence for vWF is lacking, one of skill could not reasonably conclude that agents that oppose the action of vWF would be expected to be effective in treating arterial disease.

IV. Claim Rejections under 35 U.S.C. 112, First Paragraph

Claims 70 and 71 are said not to be enabled because one of skill would not know how to obtain pro-vWF compositions at the recited purity levels. These claims have been canceled, thus rendering this rejection moot.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



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